## SUPPORT FOR THE AMENDMENTS

The claim amendments have been submitted to correct a typographical error. Accordingly, no new matter is believed to have been added to the present application by the amendments submitted above.

## REMARKS

Claims 134, 139-142, 145, 148-155, 157, 158, 160, 161, 163, 164 and 166-177 are pending. Favorable reconsideration is respectfully requested.

Claims 145, 149 and 150 have been rejected under 35 U.S.C.§ 112, second paragraph as being indefinite for the recitation of an "aimmune response." Claim 145 has been amended to "induces an immune response," which should render this rejection moot.

In view of the foregoing, withdrawal of this rejection is respectfully requested.

Claims 134, 145, 176 and 177 have been objected to since parasitemia was misspelled. These claims have been amended to correct this inadvertent typographical error, rendering this objection moot.

Claims 153, 169, 172 and 175 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Longacre (1995) in view of Longacre et al. (1994). For the following reasons, this rejection is respectfully traversed.

Longacre (1995) disclose the C-terminal sequence of a *Plasmodium cynomolgi* MSP-1 and its homology with other *Plasmodium* species. This reference does not disclose that the amino acid sequence from $Lys_{296}$ to $Ser_{380}$ as shown in SEQ ID NO:11 induces an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite.

Longacre et al. (1994) disclose recombinant proteins from *Plasmodium vivax* merozoite surface protein that have been produced in a baculovirus expression system. 42-kDA and a 19 kDA proteins were recombinantly produced, which were N-glycosylated.

Longacre et al. (1994) does not disclose or suggest that the recombinant constructs produced therein can induce an immune response, which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. Rather, immunoblotting with a pool of immune

human sera obtained by donors living in a *P. Vivax* hyperendemic region of Sri Lanka was used to only confirm that the recombinant proteins of 42 kDA and 19 kDA were recombinantly produced. However, this data is no indication that parasitemia can be inhibited *in vivo*.

Indeed, the enclosed article from Arnot et al. demonstrates that baculovirus MSP-$1_{19}$ gave superior results compared with other antigen-based malaria vaccine candidates. Baculovirus produced MSP-$1_{19}$ immunizations produce the lightest parasite-specific antibody titers in immunofluorescence assays; induced more antibodies, in ELISAs, gave the highest levels of growth inhibitor in HB3 and 3D7 parasite cultures and inhibited growth as well as or better at lower IgG concentrations. This is an unexpected result, not set forth in the cited references, and should be considered with respect to the obviousness rejection.

Moreover, neither of these two cited references suggests that the recombinant protein in Claim 153 can form oligomers when recombinantly produced, which oligomers can inhibit parasitemia *in vivo*.

In fact due to the unpredictability in this art the mere production of recombinant proteins and oligomers thereof cannot be equated with their physiologic action *in vivo* unless truly demonstrated. It is only in the present specification that it was scientifically proven that the recombinant constructs set forth in the rejected claims that the recombinant construct set forth in Claim 153, as well as the oligomers thereof can inhibit parasitemia *in vivo*.

Thus, Applicants submit that Claims 153, 169, 172 and 175 are unobvious in view of the two cited Longacre references. Accordingly, in view of the foregoing, withdrawal of this rejection is respectfully requested.

Claims 134, 139 to 141, 145, 148 to 150, 176 and 177 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Longacre (1995) in view of Longacre et al. (1994) and further in view of Holder et al. (U.S. 5,720,959). For the following reasons, this rejection is respectfully traversed.

Longacre et al. (1995) and Longacre et al. (1994) were discussed extensively above and the argument applies with respect to this rejection as well. It should be noted that neither reference suggests a vaccinating composition in which parasitemia can be inhibited *in vivo*. Moreover Longacre et al. (1995) merely discloses a sequence comparison of various *Plasmodium* species and does not disclose or suggest the production of recombinant proteins that can be used in a vaccinating composition. Longacre et al. (1994) discloses several recombinantly produced *Plasmodium vivax* MSP-1 C-terminal recombinant proteins. The rejected claims exclude any a 19 kDa C-terminal fragment MSP-1 protein from *Plasmodium vivax*. Moreover, there is no suggestion in Longacre et al (1994) to use in a vaccinating composition an anchored C-terminal. 19 kDA MSP-1 protein.

Holder et al. does not remedy the deficiencies of the primary references. U.S. patent 5,720,959 discloses recombinantly produced polypeptides having EGF-1 and EGF-2 domains. The EGF-1 domain has 48 amino acids, while the EGF-2 domain has 53 amino acids. These domains were recombinantly produced as fusion proteins in *E. coli*. To demonstrate immunogenicity another recombinantly produced EGF-1 and EGF-2 from *Plasmodium yoelii* was recombinantly produced also in *E. coli* and mice were immunized with the fusion protein GST containing EGF-1 and EGF-2 domains, as well as the recombinantly produced EGF-1 and EGF-2 domains cleaved from the fusion protein.

The mice immunized with the recombinantly produced EGF-domains in *E. coli* had little or no parasitemia after 17 days. The conclusion was that producing EGF-like domains in *E. coli* that the disulphide bonds and tertiary structure of these domains was conserved.

First of all, the claimed invention is not directed to *Plasmodium* parasites that are derived from mice. Rather the claims recite that the 19 kDa C-terminal MSP-1 protein is from a "*Plasmodium* parasite **that is infectious in man**."

Secondly, none of the recombinantly produced EGF-domains produced in *E. coli* from the *Plasmodium falciparum* clones T9/96 and T9/94 were tested for immunogenicity.

Hence the only conclusion that the skilled artisan can draw from the teachings of Holder et al. is that EGF-1 and EGF-2 domains from *P. yoelii* recombinantly produced in *E. coli* in which mice were immunized therewith appear to be protected against parasitemia for 17 days. These results cannot be equated to mean that the other constructs from *Plasmodium falciparum* induce the same results, since these EGF-domains were never used to test for immunogenicity.

Thus there is simply no suggestion or even teaching that a *Plasmodium* parasite that is infectious in man other than *Plasmodium vivax* can induce an immune response and inhibit parasitemia *in vivo* in a host infected with said *Plasmodium* parasite. Without such, demonstration in any of the cited references, or a suggestion from the combination thereof, this rejection cannot be maintained..

Finally, as set forth above unexpected results are achieved with baculovirus produced MSP-$1_{19}$, which must be considered with respect to obviousness and the teaching of prior art.

Therefore, in view of the foregoing, withdrawal of this rejection is respectfully requested.

Claims 151, 152, 154, 155, 157, 158, 160, 161, 163, 164, 166, 167, 168, 170, 171, 173 and 174 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over the combined teachings of Chappel and Holder, Miller et al., Longacre et al. (1994) and Longacre (1995). For the following reasons, this rejection is respectfully traversed.

The rejected claims are directed to specific recombinant proteins, as well as oligomers thereof.

Chappel and Holder disclose that monoclonal antibodies that inhibit *Plasmodium falciparum* invasion in vitro recognize the EGF-1 domain of MSP-1. The Examiner relies on the disclosure of S42ΔA, which contains 271 amino acids of MSP-1 from the Wellcome strain, including both EGF domains, fused to the terminal 34 amino acids of MSP-1, also from the Wellcome strain. There is no suggestion in Chappel and Holder to use another leader sequence from a different *Plasmodium* species or to limit this leader sequence to 32 amino acids. Nor is there any suggestion in this reference to construct a recombinant C-terminal MSP-1 protein that has less than 271 amino acids.

Furthermore, Chappel and Holder fail to suggest that their recombinant proteins recited therein have the ability to induce an immune response which can inhibit parasitemia *in vivo* in a host infected with a *Plasmodium* parasite. At best their conclusion of their study was speculative, as evidenced by the following statement at page 309:

> In conclusion, we have shown that the first EGF-like domain can be expressed as a fusion protein in *E. coli* and it binds growth-inhibitory antibodies; if it is possible to stimulate a strong immune response to, this polypeptide, it has potential for development into a vaccine against blood-stage malaria.

Thus, the only conclusion that can be made by the disclosure of Chappel and Holder is that the first EGF-1 domain binds growth-inhibitory antibodies. This domain was not proven at all to induce an immune response that can inhibit parasitemia *in vivo*.

Miller et al. was only cited to orient the sequences in Chappel and Holder.

Longacre et al. (1994) is directed to *Plasmodium vivax* recombinant MSP-1 proteins wherein the leader sequence and the C-terminal fragment is from *Plasmodium vivax*. There is no suggestion in this reference to interchange a different *Plasmodium* species in the C-terminal MSP-1 fragment.

Longacre (1995) compares the C-terminal MSP-1 sequences of *P. cynomolgi* with different strains of *P. vivax*. The sequence of *P. falciparum* is not disclosed in this reference.

In fact the two cited Longacre references have no disclosure or suggestion of using a *P. falciparurn* recombinant protein.

The combination of these references fails to suggest to the skilled artisan the recombinantly claimed constructs cited in this rejection, which can induce an immune response that can inhibit parasitemia *in vivo*.

As set forth above and described in Arnot et al., unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-$1_{19}$, which is an unexpected result not foreseen in the cited prior art.

Due to the unpredictability in this art, without such a showing this rejection cannot be maintained.

Therefore, in view of the foregoing, withdrawal of this rejection is respectfully requested.

Claims 134, 139 to 142, 148, 150, 176 and 177 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Chappel et al., Miller et al. and Longacre (1994) in view of Longacre et al. (1995) and further in view of Holder et al. For the following reasons, this rejection is respectfully traversed.

Chappel et al., Miller et al. and Longacre (1994) in view of Longacre et al. were discussed extensively above and these arguments apply to this rejection as well. None of these cited references suggest to the skilled artisan the recombinantly claimed constructs can induce an immune response that can inhibit parasitemia *in vivo*. Since this art is unpredictable proper experimental results must be proven, and not merely hypothesized.

Although the U.S. patent to Holder et al. does demonstrate that recombinant constructs producing EGF-1 and EGF-2 domains from *P. yoelii* stimulate a protective immune response in mice no demonstration was made that the recombinant EGF-domain constructs directed towards *P. falciparum* attain the same protection.

The combination of these references fails to suggest to the skilled artisan the recombinantly claimed constructs cited in this rejection, which can induce an immune response that can inhibit parasitemia *in vivo* in a host transfected with a *Plasmodium* parasite and wherein said *Plasmodium* parasite is infectious in man.

As set forth above and described in Arnot et al., unexpected results of enhanced parasite-specific antibody titers, a larger induction of antibodies and higher levels of growth inhibition were achieved with baculovirus produced MSP-$1_{19}$, which is an unexpected result not foreseen in the cited prior art.

Applicants thus submit that the presently claimed invention is unobvious in view of the cited prior art.

Accordingly, in view of the foregoing, withdrawal of this rejection is therefore respectfully requested.

Applicants submit that the present application is in condition for allowance. Early notice to this effect is earnestly solicited.

Respectfully submitted,

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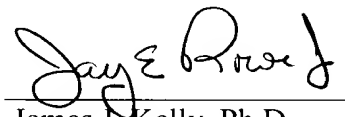

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